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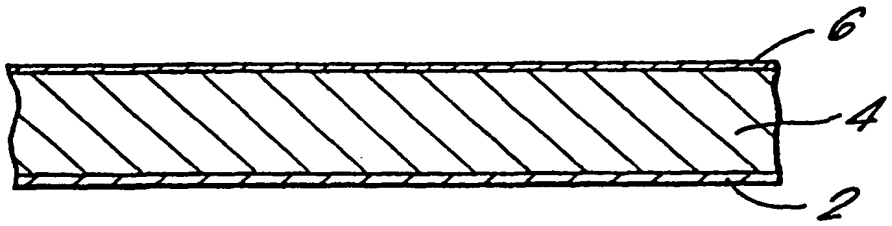
(54) Title: TRANSDERMAL DRUG DELIVERY SYSTEM



(57) Abstract

In a method of manufacturing such a system, an active substance is dissolved in a ratio less than saturation level in a solvent which is also a skin penetration enhancer. The system (4) is coated as a layer onto a siliconized release paper (2) and laminated onto a backing strip (6).

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TITLE

Transdermal Drug Delivery Systems

DESCRIPTION

Technical Field

The invention relates to transdermal drug delivery systems, that is systems for the administration of medicine through the skin of a patient and into the systemic circulation. In this way, the medicine avoids passing through the gastro-intestinal tract and liver. Thus metabolism is to some extent avoided, and a smaller dose can be used.

Background Art

GB 2249956 contains a useful summary of the state of the art, and discloses such systems containing super-saturated solutions of an active ingredient within an adhesive layer by use of a carefully selected mixture of solvents.

THE INVENTION

The invention provides a method of manufacturing a transdermal drug delivery system which comprises dissolving a pharmaceutically active substance in a ratio less than saturation level in a solvent which is also a skin penetration enhancer, and mixing the resulting solution with an adhesive in the form of an aqueous dispersion or solution. By using the active substance in a ratio less than saturation level, there is a reduced risk of crystallization, a stable system can be manufactured, and a constant rate of delivery to the patient obtained.

It is surprising that certain solvents act both as a skin penetration enhancer and as a solvent for the active substance. Such solvents include crotamiton, diethyltoluamide (DEET) and mixtures of two or more thereof. The ratio of crotamiton to diethyltoluamide in such a solvent mixture may be from 5:95 to 95:5% by weight of the total enhancer/solvent content depending on the delivery rate and extent of delivery required for the active substance. By choosing a solvent or solvents having a boiling point higher than any drying temperature applied to the system, and controlling the drying temperature, the solvent(s) do not evaporate, the solution of the active substance never becomes saturated, and a high proportion of active substance remains in the

system. The active substance/solvent(s) solution can be maintained at 20°-30°C for over one month.

The system is generally presented on a backing sheet and protected up to use by a release liner.

The pharmaceutically active substance may be:
α-Adrenergic agonists such as Adrafinil, Adrenolone, Amidephrine, Aproclonidine, Clonidine, Ephedrine, Naphasoline and Tramazoline;
ß-Adrenergic agonists such as Albuterol, Clenbuterol, Clorprenaline, Methoxyphenamine and Terbuterol;
α-Adrenergic blockers such as Amosulalol, Dapiprasol, Ergoloid Mesylates, Prazosin, Terazosin, Yohimbine;
ß-Adrenergic blockers such as Acebutolol, Alprenolol, Atenolol, Pindolol, Propanolol and Timolol;
Anabolics such as Androstenediol, Ethylstrenol, Methandriol, Nandrolone, Oxymesterone, Quinbolone and Stenbolone;
Analgesic (narcotic) such as Alfentanil, Benzylmorphine, Buprenorphine, Codeine, Codeine Phosphate, Dihydrocodeine, Dihydromorphine, Fentanyl, Methadone Hydrochloride, Morphine, Morphine Derivatives, Narceine, Opium, Oxycodone, Oxymorphone, Phenazocine and Sufentanil;
Analgesics (non-narcotic) such as Acetaminophen, Acetanilide, Acetylsalicyclic Acid, Carbamazepine, Diflunisal, Indomethacin, Ketoprofen, Naproxen, Phenacetin, Salicylamide and Tramadol;
Androgens such as Mesterolone, 17-Methyltestosterone, Testosterone and Testosterone Propionate;
Anaesthetics such as Amylocaine Hydrochloride, Bupivacaine, Lidocaine, Midazolam, Procaine, Tetracaine Hydrochloride, Thiopental Sodium and Zolamine;
Anti-acne drugs such as Algestone Acetophenide, Benzoyl Peroxide, Cyproterone, Resorcinol, Retinoic Acid and Tetroquinolone;
Anti-amebic such as Chloroquine, Chlortetracycline, Dehydroemetine, Emetine, Teclosan, Thiocarbamizine and Tinidazole;
Antianginals such as Alprenolol, Amlodipin Diltiazem, Felodipine, Isosorbide Dinitrate, Nicardipine, Nifedipine, Nitroglycerin, Oxprenolol, Pindolol, Timolol and Verapamil;

Antibacterial drugs such as Gentamicin, Kanamycin, Neomycin, Chloramphenicol, Chloramphenicol Pantothenate, Clindamycin, Lincomycin, Clarithromycin, Erthromycin and Cycloserine;
Anti-estrogens such as Delmadinone Acetate, Tamoxifen and Toremifene;
Antifungal drugs such as Clotrimazole, Econazole, Ketoconazole, Miconazole and Potassium Iodide;
Antihistamines such as Chlorpheniramine, Dimethindene, Pheniramine, Triprolidine and Phenothiazine;
Antihypertensive drugs such as Captopril, Enalapril, Clonidine and Minoxidil;
Anti-inflammatory drugs such as Mefenamic Acid, Flubiprofen, Ibuprofen, Indomethacin, Ketoprofen, Aspirin, Mesalamine, Olsalasine, Piroxicam and Tenoxicam;
Anti-parkinsonian drugs such as Amantadine, Levodopa, Pergolide and Pridinol;
Antipyretics such as Camphor, Menthol, Phenol, Polidocanol, Spirit of Camphor and Trimeprazine;
Anti-seborrheic drugs such as Pyrithione, Resorcinol, Selenium Sulphides and Tioxolone;
Antiseptics such as Chlorhexidine, Bismuth Iodide Oxide, Povidone Iodine, Triclosan, Triclosane Potassium, Carvacrol, p-Cresol, Chloroxine, Halquinol, Boric Acid, α-Terpineol and Chlorhexidine;
Anti-ulcerative drugs such as Cimetidine, Enprostil, Omeprasol, Ranitidine and Trimoprostil;
Anxiolytic drugs such as Buspirone, Bromazepam, Diazepam, Loxapine, and Meprobamate;
Chlorinergic agents such as Bethanechol Chloride, Physostigmine and Pyridostigmine Bromide;
Depigmentors such as Hydroquinine, Hydroquinone and Monobenzone;
Estrogens such as Benzestrol, Dienestrol, Diethylstilbestrol, Dimestrol, Methestrol, Conjugated estrogenic Hormones, Equilenin, Equilin, Estradiol, EstradiolBenzoate, Estradiol 17ß-Cypionate, Estriol, Estrone, Ethinyl Estradiol, Mestranol, Moxestrol, Quinestradiol and Quinestrol;
Gonadotropic hormones such as LH and PMSG;
Nootropic agents such as Aceglutamide, Antiracetam, Piracetam, Pyritinol and Tacrine.
Progestogens such as Allylestrenol, Anagestone, Chlormadinone Acetate, Delmadinone Acetate, Demegestone, Desogestrel, Dimethisterone,

Dydogesterone, Ethisterone, Ethynodiol, Flurogestone Acetate, Gestodene, Gestodene Caprolate, Haloprogesterone, 17-Hydroxy-16-methylene-progesterone, 17α-Hydroxyprogesterone, 17-α-Hydroxygesterone Caprolate, Lynestrenol, Medrogestone, Medroxyprogesterone, Megestrol Acetate, Melengestrol, Norethisterone, Norethisterone Acetate, Noretynodrel, Norgesterone, Norgestimate, Norgestrel, Norgestrienone, Norvinistyerone, Pentagestrone, Progesterone, Promegestone, Quingestrone and Trengestone;
Respiratory stimulants such as Almitrine, Doxapram, Lobeline, Sodium Succinate and Tacrine;
Vitamins, vitamin sources and vitamin extracts such as Vitamins A, B, C, D, E and K and derivatives thereof, Calciferols, Glycyrrhiza and Mecobalamin; or
Vulnerary agents such as Acetylcysteine, Allantoin, Asiaticoside, Cadexomer Iodine, Chitin, Dextranomer and Oxaceprol.

The solvent can be Crotamiton, Diethyltoluamide (DEET), Transcutol (Diethylene glycol monoethyl ether), Labrafil MI944CS (unsaturated polyglycolysed glycerides), Labrasol (Glyceryl and polyethylene glycol esters), Tea-tree oil (Oil of Melaleuca), Propylene Glycol, MP DIOL (2-Methyl-1,3- Propanediol) or Polyetheylen Glycol.

It will be appreciated that the amount of active substance to be incorporated in the delivery system is dependent or governed by the drug composition and/or concentration, the desired therapeutic effect for a patient, and the period for which the delivery system is to provide a therapeutic drug level. Preferably, the active substance is present in an amount from 0.1% to 50% by weight of the coating material (i.e. an aqueous emulsion or adhesive solution). More preferably, 0.3% to 30% by weight of the coating material.

The adhesive can be an acrylate, silicone or polyisobutylene. The active substance is generally incorporated in the solvent/enhancer at room temperature (25°C or below) and in a ratio less than 90% of saturation level to prevent crystal formation during storage. Dissolution may be aided by sonication or warming. The resulting solution can be added slowly to the adhesive which may be in the form of an aqueous dispersion or solution, and mixed. An adhesive thickener may be added

to the mixture at about a 50% solution/water mix to produce a thicker spreading solution for reverse roll coating or knife over roll coating.

The resulting delivery system may then be coated onto a release liner, which may be a siliconised polyester such as type FL 2000 (commercially available), or paper, which naturally is impermeable to the active substance. The system can then be dried by circulating hot air, and laminated onto a backing sheet, which may be a 3M Health Care Type 1220, the backing sheet naturally being impermeable to the active substance. The layer may be coated to a wet-coat thickness of from 20 to 500μ. Alternatively, the delivery system mixture may be spread or coated onto the backing sheet, and then laminated to the release liner. The hot air circulation may be effected at gradually increased temperatures from 50°C to 140°C.

DRAWING

Fig. 1 is section through an adhesive tape for application to the skin of a patient comprising a drug delivery system according to the invention. A delivery system comprising an active substance, adhesive and solvent/skin penetration enhancer 4 is coated as a layer onto a siliconized release paper 2 and laminated onto a backing strip 6.

The following Examples of ingredients in parts by weight may be used in the production of delivery systems as described above:

	Eg 1	Eg 2	Eg 3	Eg 4	Eg 5
Esterol Hemihydrate	1.0	1.0	1.0	1.0	0.9
Norethisterone Acetate	2.0	2.4	2.4	2.4	2.4
DEET	-	-	-	18.0	15.3
Crotamiton	-	18.0	20.0	-	2.7
Labrafil M (1944CS)	5.0	4.25	-	-	-
Transcutol	20.0	-	-	-	-
Lauroglycol	4.0	-	-	-	-
Labrasol	4.0	-	-	-	-
Monsanto 3011	64.00	74.35	-	-	-
Monsanto 2484			76.6	78.6	-
Monsanto 2397	-	-	-	-	-
C945/127		-	-	-	78.7
NS 2287	-	-	-	-	-
Acrysol ASE60	-	-	-	-	-
Ammonia BP (aq.dil)	qs	qs	qs	qs	-
Purified water (BP)	qs	qs	qs	qs	qs

	Eg 6	Eg 7	Eg 8	Eg 9	Eg 10	Eg 11
Estradiol Hemihydrate	0.9	0.9	0.9	1.2	1.1	1.0
Norethisterone Acetate	2.4	2.4	2.4	-	-	-
DEET	9.0	2.7	15.3	-	6.0	6.09
Crotamiton	9.0	15.3	2.7	7.5	0.6	-
Labrafil M(1944CS)	-	-	-	2.0	-	-
Transcutol	-	-	-	-	-	-
Lauroglycol	-	-	-	-	-	-
Labrasol	-	-	-	-	-	-
Monsanto 3011	-	-	-	-	-	-
Monsanto 2484	-	-	-	-	-	-
Monsanto 2397	-	-	-	89.3	-	-
C945/127	78.7	78.7		-	-	93.77
NS 2287	-	-	78.7	-	92.3	-
Acrysol ASE60	-	-	-	-	-	0.2-0.9
Ammonia BP (aq.dil)	-	-	-	-	-	qs
Purified water (BP)	qs	qs	qs	qs	qs	qs

Manufacturing Method (illustrative)

A) Delivery System using adhesive - aqueous emulsion

The active substance is dissolved in the solvent by means of heating and mixing over a 45°-55°C water bath with agitation. When the solution is optically clear, it is checked microscopically for absence of crystals.

The adhesive is weighed into a separate mixing vessel, diluted with water if necessary over a period not exceeding 30 mins to achieve the requisite viscosity. The active substance/solvent solution is gradually added to the adhesive solution with mixing. The pH is adjusted to 6.5-7.5 and a thickener is added (if appropriate) to obtain a suitable viscosity (eg 900-100 cps) for the selected coating process such as reverse roll coating or knife over roll coating.

The resultant aqueous emulsion is coated onto a release liner (typical coating thickness 20-500 μ), and dried by passing in sequence through ovens at 50-140°C. The product is then laminated onto a backing sheet.

B) Delivery system using an adhesive solution

The active substance is dissolved in a solvent by means of heating and mixing as described above. The adhesive is weighed in a separate vessel and the active substance/solvent solution is gradually added to the solution of adhesive with mixing. The resultant adhesive solution is coated onto a release liner, dried by passing in sequence through ovens at 50-140°C. The product is then laminated onto a backing sheet.

In-vitro drug delivery through the skin

In-vitro skin permeation experiments with human skin have been on systems made from the above ingredients carried out using Franz-type diffusion cells, and the studies were carried out on a Hanson Microette system.

Dermatomed human skin sections were mounted onto the Franz cells and transdermal drug delivery systems mounted on tape backings (1.5cm^2) were placed on the stratum corneal surface of the skin. Each Franz cell contained 7ml of ethanol phosphate buffered saline as the receptor medium, maintained at 32°C. At predetermined time intervals 0.7ml of the receptor solution was sampled and an equal amount replaced.

The samples were analysed by High Pressure Liquid Chromatography.

The skin mass transport of Estradiol and Norethisterone Acetate has been found to be enhanced by the solvent/skin penetration enhancer DEET and/or Crotamiton in a concentration below saturation. Further, the active substance flux profile follows the solvent flux profile, the latter showing high skin penetration flux during the first 20 hours of application.

Indications

The main indications are in both peri-menopausal and menopausal women for the control in the former of the symptoms of the menopause such as hot flushes, sweating and the other symptoms of the peri-menopause,

and in the case of the menopause the prevention of osteoporosis and cardiac events such as coronary thrombosis.

CLAIMS

1. A method of manufacturing a transdermal drug delivery system which comprises dissolving a pharmaceutically active substance in a ratio less than saturation level in a solvent which is also a skin penetration enhancer, and mixing the resulting solution with an adhesive in the form of an aqueous dispersion or solution.

2. A method according to claim 1 in which the solvent/enhancer includes crotamiton.

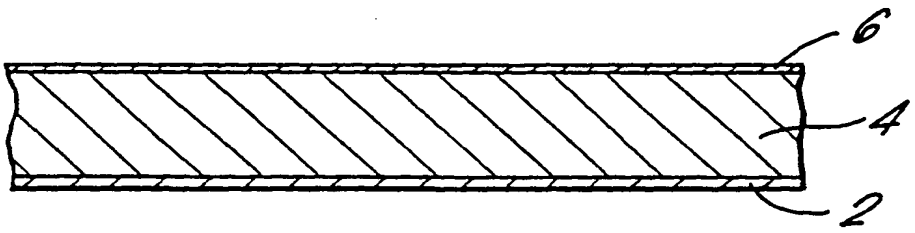
3. A method according to claim 1 or claim 2 in which the solvent includes DEET.

4. A method according to any preceding claim in which the active substance includes estradiol.

5. A transdermal drug delivery system manufactured by a method according to any preceding claim.

6. A transdermal drug delivery system according to claim 5 in which the active substance is present in said aqueous dispersion or solution from 0.1% to 50% by weight.

FIG. 1.



INTERNATIONAL SEARCH REPORT

[redacted]onal Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/70

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Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	WO 92 05811 A (ETHICAL PHARMACEULS LIMITED) 16 April 1992 (1992-04-16) the whole document & GB 2 249 956 A cited in the application	1-6
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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